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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Michael R. Rosen

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EXAMINER

SINGH, ANOOP KUMAR

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/757,827	Applicant(s) ROSEN ET AL.	
	Examiner Anoop Singh	Art Unit 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 May 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 20,49, 51-56-57,59,65-67 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 20,49, 51-56-57,59,65-67 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>5/2/2008</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Applicants' amendment to the claims filed May 2, 2008 have been received and entered. Applicants have amended claims 20 and 65, while claims 1-19, 21-48, 50, 52-55, 58 and 60-64 have been canceled. Claims 20, 49, 51, 56-57, 59, 65-67 are pending in this application.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/2/2008 has been entered.

Election/Restrictions

Applicant's election with traverse of the invention of group IV (claims 20, 23-38, 49-50 and 64) filed on October 24, 2005 was acknowledged. Applicant's argument of examining method for treating cardiac condition using composition of for ion channel transfer comprising stem cell modified with a compound (group VI, claim 51-62) with elected group was found persuasive, therefore invention of group IV and VI directed to composition and method of treating cardiac condition were rejoined for the examination purposes.

Claims 20, 49, 51, 56-57, 59, 65-66 and 67 are under consideration in the instant application.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 5/2/2008 has been considered by the examiner.

Declaration

The Rosen declaration filed on May 2, 2008 under 37 CFR 1.132 is sufficient in part to overcome the rejection of claims 49, 51, 56-57, 59 and 65-67 under 35 U.S.C. 112 First paragraph. The declaration will be discussed in detail below as it applies to the rejection.

Maintained in modified form-Claim Rejections- 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49, 51, 56, 57, 59, 66-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

(i) a method of expressing a functional HCN2 ion channel in the mammalian heart, said method comprising, site specifically introducing the composition comprising a mesenchymal stem cell incorporated with a nucleic acid which encodes HCN2 ion channel in an amount sufficient to create an ion channel in the cell; wherein said composition is directly introduced by injection into the heart, microinjection or cardiac catheterization; such that said composition forms gap junction with the cells of the heart; thereby expressing the functional ion channel in the mammalian heart,

(ii) a method of inducing a pacemaker current in a mammal's heart, said method comprising, site specifically introducing a composition comprising a mesenchymal stem cell incorporated with a nucleic acid which encodes HCN2 ion channel in an amount sufficient to create an ion channel in the cell; wherein said composition is directly introduced by injection into the heart, microinjection or cardiac

catheterization; such that said composition forms a gap junction with the cells of the heart; thereby inducing a pacemaker current in the cells of the heart,

(iii) a method of inducing pacemaker current in a cardiomyocyte, said method comprising, contacting a cardiomyocyte with a composition comprising a mesenchymal stem cell incorporated with a nucleic acid which encodes HCN2 ion channel in an amount sufficient to create an ion channel in the cell; wherein said composition is contacted by injection into the heart, microinjection or cardiac catheterization; wherein said composition forms gap junction with the MSC; thereby inducing a pacemaker current in the cardiomyocyte,

does not reasonably provide enablement for a method for treating any cardiac rhythm disorder or topical administration to cells of the heart for treating, expressing or inducing current in the heart. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicant's amendments and declaration by Dr. Rosen on May 3, 2008 have been fully considered and are persuasive to the extent claims read on a method of expressing functional HCN2 ion channel in a mammalian heart by directly injecting the composition by injection, microinjection or cardiac catheterization. Therefore, rejection to these issues with respect to claims 49, 57, 59, 66 and 67 are withdrawn. However, applicants' argument that instant claims are enabled for treating a cardiac rhythm disorder in a mammal or introducing the composition topically was found not persuasive.

Applicants argue that HCN2 channel was well known and the specification teaches the sequences of HCN2 (see paragraphs 37, 48 of the specification). Further, the specification teaches a person skilled in the art methods for isolation of homogeneous populations of MSCs, nucleic acids encoding the HCN2 channel that may be expressed in MSCs to induce or regulate a pacemaker current therein, and the use MSCs expressing a pacemaker ion channel to induce a pacemaker current in

a heart. Applicants assert that specification provides a working example of the delivery into a canine heart of hMSCs transfected with a nucleic acid encoding a HCN2 polypeptide, resulting in the expression of functional HCN2 channels and the generation of a stable, idioventricular pacemaker rhythm in the canine heart. (See para. 0029 and Fig. 10). Applicants argue that the specification teaches a person skilled in the art methods for isolation of homogeneous populations of MSCs, nucleic acids encoding the HCN2 channel that may be expressed in MSCs.

Applicant's arguments have been fully considered but are not fully persuasive. Applicants arguments of claims directed to a method of using MSCs for expressing a pacemaker ion channel or inducing a pacemaker current in the heart is not rejected and therefore arguments pertaining to these issue are moot as these embodiments were indicated as enabled in previous office action.

In response, it is noted that that the issue is not whether one of skilled in the art could isolate MSC or prepare homogenous populations of MSC for inducing a pacemaker current rather the issue is whether the resulting method would treat a cardiac rhythm disorder in a mammal. In the instant case, claims are directed to a method of site specifically introducing into the mammal's heart a composition comprising MSC incorporated with HCN2 in an amount sufficient to form gap junction with the cell of mammalian heart. The guidance provided in the specification is limited to human mesenchymal stem cells transiently transfected with mH2-EGFP (See Figure 7) that could generate pacemaker current (Figure 8), which when implanted via a 21-gauge needle into the anterior left ventricular wall of the dog generate idioventricular pacemaker rhythm in the canine heart (see figure 10 A-E). However, inducing a pacemaker current or expressing functional ion channel for some time does not extrapolate to treating cardiac rhythm disorder. Examiner has previously indicated that prior to the instant invention use of the instantly disclosed strategy had a number of potential limitations. One limitation relates to the possible differentiation of the MSCs within the heart into unwanted

cell lineages, such as bone and cartilage, long term survival of the grafted cell and level of transgene expression within the grafted cells (see Gepstein Expert Opinion Biol Ther, 5(12): 1531-1537, 2005 art of record, page 1534, col. 1, para. 3). These issues are particularly important for claims 51 and 52 that embrace treating a cardiac rhythm disorder in any mammal which is different in scope as compared to merely inducing a pacemaker current in heart that may or may not have potential benefit. In fact, in a related post filing art Gaudette et al (WO/2008/011134, dated 07/20/2007) concurs with this assertion and states "mesenchymal stem cells can be used as a vehicle for gene delivery to the cardiac syncytium, however, one significant drawback to the use of such cells is their ability to differentiate into different cell types of osteogenic, chondrogenic or adipogenic lineages (see para 3). Given that electrophysiological properties of hMSCs are heterogeneous, it is reasonable to assert that it would be uncertain whether hMSCs after transplantation will further differentiate into cardiac or even non-cardiac cells with electrical properties different from those of pre-transplanted cells as per teaching the teaching of Xu (also see Circulation. 112(6):e82, 2005 page 82, col. 2, last para). The specification failed to provide guidance with respect to differentiation potential of the MSC that could adversely impact the outcome in a treatment method. This assertion is supported in numerous prior art including one cited by Examiner that describes induction of arrhythmias after stem cell transplantation by several mechanisms including electro-tonic stimulation of cardiac cells, electrical heterogeneity of action potentials during stem cell differentiation process, increased nerve sprouting, and local tissue injury induced by intra-myocardial injection (see Mocini et al, Ital Heart J. 2005; 6(3): 267-71, art of record). It is emphasized that contrary to applicant's assertion these are not safety or efficacy issues; instead these are potential limitations of transplanting stem cell including differentiation of MSC into any tissue. The specification has not provided adequate guidance with respect to how an MSC population that does not differentiate into cells of other

lineages will be obtained for transplanting into heart. An artisan would have to perform undue experimentation to make and use the invention without reasonable expectation of success.

Applicants argue that Plotnikov (Circulation 116:706713, 2007) includes experimental details that are described in the specification and a person of ordinary skill in the art could have reduced to practice without undue experimentation by readily determining the appropriate concentration of MSC cells which would be effective in the treatment of a particular cardiac disorder or condition. Applicants also argue that treatment is defined as medical management of a patient which is different from cure (see page 8 of the argument). Applicants assert that treating or inducing pacemaker current is not unpredictable. Applicants cites Plotnikov (Circulation 116:706713, 2007) to show that no differentiation was observed over 42 days and there was no humoral or cellular rejection (see page 9). Applicants also argue that dog model disclosed in the specification is recognized model for the human heart (see page 12).

In response, it is noted that prior to instant invention, adult stem cell including MSC therapy was limited due issues relating to the number and distribution of the surviving grafted cell within the heart, and the degree of coupling between host and donor cells that may have important consequences to the function of these cells (see Gepstein et al Expert Opinion Biol Ther, 5(12): 1531-1537, 2005). Grinnemo et al also indicated the potential of graft rejection in a xenogenic model when adult hMSC is transplanted (see Grinnemo et al J Thorac Cardiovasc Surg. 2004 May; 127(5):1293-300, page 1298, col. 2, last para). In spite of applicants assertion that effect of dose of stem cell is routine optimization, state of the art effectively summarized by the reference of de Silva et al (Cytotherapy. 2004; 6(6): 608-614) teaches that the optimal cell preparation for each of the variety of potential cardiovascular applications remains to be determined. It cannot be assumed that one cell preparation will be equally efficacious for all applications, and different cell

preparations may have varying profiles while exacerbation of atherosclerosis, arrhythmogenesis, inappropriate calcification and local or ectopic tumor formation are some other limitation. In fact, applicants themselves address three main issues that are frequently raised in biological pacemaker art in post filing art that included (i) "dose" of stem cells that might provide adequate pacemaker function, (ii) cells that generate stable pacemaker function and catecholamine responsiveness, and (iii) stem cell survival. Even one agrees with applicant's assertion that appropriate concentration of MSC cells in the treatment of a particular cardiac disorder or condition may be routine optimization. It is reasonable to raise issue with respect to graft rejection. Although, Plotnikov (Circulation 116:706713, 2007) in post filing art provided survival of graft up to 42 days, however, instant specification does not provide any guidance with respect to binding of canine IgG to the surface of hMSCs (as shown in Plotnikov Figure 6D) or contemplated measuring infiltration by CD3⁺ T lymphocytes (Figure 6E) to establish whether or not method of claims 51 and 56 that read on xenogenic transplant would survive in a method of treating any rhythm disorder in a mammal. MPEP 2164.05(a) states "The state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date. *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1325-26 (Fed. Cir. 2004) ("a patent document cannot enable technology that arises after the date of application"). Publications dated after the filing date providing information publicly first disclosed after the filing date generally cannot be used to show what was known at the time of filing. *In re Gunn*, 537 F.2d 1123, 1128, 190 USPQ 402,405-06 (CCPA 1976); *In re Budnick*, 537 F.2d 535, 538, 190 USPQ 422, 424 (CCPA 1976). It is noted that several years after filing of this application, Plotnikov emphasizes that MSC have the potential to differentiate into more mature cell types. Plotnikov states "If this occurs, it is reasonable to question whether the cells will maintain their immunoprivileged status. Given this possibility, it is important to ensure that

hMSCs remain in an undifferentiated state for use as biological pacemakers and/or that evidence be obtained to determine whether maturation and differentiation cause immunoprotection to be lost and rejection to occur". Thus, it is apparent that the disclosure in the specification at best is limited to a method of expressing a functional HCN2 and a method of inducing pacemaker current in heart. The specification fails to extrapolate these finding to a method of treating cardiac rhythm disorder as several issues including graft survival and conditions that would exclude MSC potential to differentiate into other mature cell types were not resolved at the time of filing of this application.

With respect to applicants argument that instant claims are directed to treating and not curing the cardiac rhythm disorder, it is emphasized that claims as recited are broad and embrace at least one of conduction block, complete atrioventricular block, incomplete atrioventricular block or sinus node dysfunction. It is generally known in the art that Atrioventricular (AV) block could be partial or complete interruption of impulse transmission from the atria to the ventricles. This may be caused by variety of condition including idiopathic fibrosis and sclerosis of the conduction system, ischemic heart disease due to drugs; increased vagal tone; valvulopathy; or congenital heart, genetic, or other disorders such as cardiac lymphoma (see Tai et al Japanese Journal of Clinical Oncology 31, 217-220, 2001). In certain instance such as congenital complete AV block pacing of heart is not well defined and not resolved (see Kertesz et al Tex Heart Inst J 1997, 24, 301-307). Furthermore, complete AV block may have 1st, 2nd or 3rd degree AV block. In a post filing art Church et al (Journal of Veterinary Cardiology, 2007, 9, 53-57) teaches that the majority of cases of third degree atrioventricular (AV) block in dogs is idiopathic and is characterized by non-specific fibrotic changes in the AV node. Church et al report a case of third degree AV block with ventricular arrhythmias secondary to acute lymphocytic-plasmacytic myocarditis that resulted in sudden death shortly after permanent pacemaker implantation. Church reported that

histologic evidence of myocarditis is found in approximately 6% of cases of third degree AV block in humans, while histopathological changes associated with AV block are not well documented in dogs. Church also teaches a case of fatal severe lymphocytic-plasmocytic myocarditis that is associated with severely elevated serum cardiac troponin I levels and sudden death following pacemaker implantation. Church concludes the overall incidence of myocarditis-related complete AV block in dogs requires further investigation (see page 55, Discussion and page 56, col.2, last para.). With respect to applicants' argument and declaration by Dr. Rosen that dog model disclosed in the specification is recognized model for the human heart, examiner would agree with the applicant that canine model have similar characteristics as human heart. However, the vagal stimulation in canine may be enabling disclosure to a method of inducing current that may have beneficial effect (as in claims 57 and 66) , but it is not sufficient enablement for applicant's broadly claimed invention of treating cardiac rhythm disorder of varying degree of complete AV block or sinus nodal dysfunction of different etiology as discussed in preceding section. In the instant case, specification does not provide any guidance with respect to biochemical (troponin I) or histopathological (fibrotic changes in the AV node) changes in the canine model that mimic all different type of cardiac rhythm disorder embraced by the breadth of the claims. There is no evidence on record whether a pacemaker gene inserted into proximal conduction system would create a functioning biological pacemaker which can drive the ventricle in demand mode when the sinus node signal fails particularly since onset of pacemaker function after a pause following the last intrinsic beat is a critical factor (see Rajesh et al Indian pacing and Electrophysiology Journal, 2006, 6(1) 1-5). Absent of evidence to the contrary, it is not clear that delivery of genetically modified MSC to the heart of complete AV block caused by congenital heart, genetic or myocarditis-related complete AV block or other sinus node dysfunction would result in treatment of broadly recited rhythm disorder. The art of record at the time

of the invention does not provide enabling support for the claimed method of treating genus of rhythm disorder with different etiology and pathology. An artisan would have to perform undue experimentation to empirically perform the method in different animal model to test if claimed composition could treat conditions embraced by the breadth of instant claims without reasonable expectation of success.

On page 10, applicants argue that safety issue raised by the Examiner fall within the province of the Food and Drug Administration and not USPTO. Applicants also argue that the fact that inflammation might occur when the claimed methods are practiced does not mean that the claimed methods are so unpredictable as to be not enabled. In response, the issue pertaining to inflammation is withdrawn to the extent claims read on inducing current in heart, however, inflammation due to graft rejection is relevant concern in treating cardiac rhythm disorder. As stated in pervious office action, Examiner has no intention to raise any toxicity or safety issue arising from cell transplantation. The discussion is merely intended to address problems that are associated with stem cell therapy and observed by many different investigators (see art of records). The issue is particularly important with respect to treating cardiac arrhythmic disorder, since an arrhythmic episode or graft rejection after cell therapy would be contrary to the teaching and claimed method of treating any cardiac rhythm disorder.

Applicants argument and declaration by Dr. Rosen that other routes of delivery or administration, including microinjection, and catheterization were known in the prior art and disclosed in the specification is persuasive. Therefore applicant's argument with respect to delivering composition of the invention to heart for expressing functional HCN2 or inducing pacemaker current in heart by wherein said composition is introduced by injection into the heart, microinjection or cardiac catheterization is moot in view of enabling scope indicated for the claims 49, 57, 59, 66 and 67. However, rejection to delivering genetically modified MSC by

topical application to the heart is maintained for the reasons for record. Applicants are requested to indicate the section of Strauer et al (Circulation, 106, 2002, art of record) that shows delivering stem cell by topical application to the heart was routine in art. Although, declaration and Strauer reference provide adequate guidance with respect to injection or catheterization, however, there is no evidence of delivering cells by topical application to achieve intended effect particularly since cell loss after transplant is major limitation of any cell transplantation (Bartune et al (Am J Physiol Heart Circ Physiol 292: H1095-H1104, 2007, art of record). The specification does not provide any guidance with respect to delivering the composition of the invention via topical application to the heart that would result in engraftment of cells in appropriate number to induce current or treat physiologic rhythm caused by any reason as embraced by the breadth of the claims.

Withdrawn-Claim Rejections-Necessitated by amendments - 35 USC § 112

Claims 20 and 65 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of amendments to the claims.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 20, 49, 57 and 65-67 rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al (US patent application 20040087528, dated 5/6/2004, effective filing 4/24/2002); Marban et al (US Patent application Publication no US2004/0254134, publication date 2/16/2004; effective filing date 2/29/2002, art of record); Jansen et al (US Patent no 6979532, dated 12/27/2005, effective filing date 2/12/2000, art of record); Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005) is withdrawn in view of applicants' argument. Upon further consideration a new rejection is made and presented below.

Claims 20 and 65 rejected under 35 U.S.C. 103(a) as being unpatentable over Marban et al (US Patent application Publication no US2004/0254134, publication date 2/16/2004; effective filing date 2/29/2002, art of record); Jansen et al (US Patent no 6979532, dated 12/27/2005, effective filing date 2/12/2000, art of record); Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005) and Ruhparwar et al (Eur J Cardiothorac Surg. 2002; 21(5): 853-7, IDS) is withdrawn in view of applicants' argument. Upon further consideration a new rejection is made and presented below.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 20 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pittenger et al (US 6,387,369, dated 2002, ref of record), Jansen et al (US 6,979,532, dated 12/27/2005, effective filing date 2/12/2000, art of record) and Wang et al (J Thorac Cardiovasc Surg. 2000; 120(5): 999-1005, art of record).

Claims are directed to a composition comprising a mesenchymal stem cell that is genetically modified with a nucleic acid encoding HCN2.

Pittenger et al teach genetically modifying mesenchymal stem cells to express varieties of genes of interest, using viral or non-viral vectors (see col.2, lines 51-65). Although, Pittenger embraced the potential of genetically modified mesenchymal stem cells in cardiac repair, but he differed from claimed invention by not explicitly teaching transfecting cells with nucleic acid encoding HCN2.

Jansen et al cure the deficiency of Pittenger et al by disclosing a process comprising providing mammalian cells that express a hyperpolarization-activated cation channel including HCN2 and determining the membrane potential of the cells (col. 5, lines 5-25, col. 5, lines 60-63 and claims 1, 21 and 31). Additionally, Jansen et al teach a method for identifying substances that modulate the activity of hyperpolarization-activated cation channels using genetically modified mammalian host cells that express HCN2 (See col. 57-58). However, Jansen et al do not explicitly teach a transfecting HCN2 in MSC.

Wang et al provided guidance with respect to administration of MSC in the heart shows growth potential in a myocardial environment and indicated the formation of gap junctions (see abstract and Figure 6). However, Wang et al do not teach composition-comprising MSC comprising HCN2.

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the composition disclosed by Pittenger with Jansen by substituting the gene of interest in the transformed mesenchymal stem cells with HCN2. One of ordinary skill in the art would be motivated to do use different isoforms of HCN including HCN2 as Jansen had already shown that HCN2 could be expressed in mammalian cells to determine membrane potential. One of ordinary skill in the art would reasonably conclude that the composition would implicitly form gap junction when directly administered to the heart of a subject particularly since Wang taught hMSCs engrafts in the myocardium and forms gap junction with recipient cells (supra). Therefore, given that MSC were available for use to express gene of interest as per the teachings of Pittenger it would have obvious for one of ordinary skill in the art to use HCN isoform including HCN2 to produce transformed cells as disclosed in the instant application. One who would practice the invention would have reasonable expectation of successfully practicing the composition comprising mesenchymal stem cell incorporated with HCN2 or other ion channel gene because the art had already shown that HCN2 and other ion

channel isoform could be expressed in mammalian cell. One of skill in the art would have had a reasonable expectation of success in combining the teachings of Pittenger et al with those of Jansen et al and Wang because it was routine in the art at the time of filing to genetically modify mesenchymal stem cells by substituting the coding sequence of one transgenes with an other gene of interest.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

Maintained- Double Patenting

Claims 20, 49, 51, 56-57, 59, 65-66 and 67 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 12, 39, 65-75 of copending Application no 10/342506 (US Patent Publication no 20040137621). Even though the conflicting claims are not the same, they are not patentably distinct from each other because both sets of claims encompass similar composition and method steps of inducing current and /or treating a cardiac condition by introducing a composition of mesenchymal stem cell comprising a nucleic acid encoding HCN2 into a subject.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. As indicated by applicants a Terminal disclaimer later would obviate this rejection.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164

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USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh
AU 1632

/Peter Paras, Jr./
Supervisory Patent Examiner, Art Unit 1632